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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,604	12/07/1999	GIOVANNI ABATANGELO	515-4181	1155

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EXAMINER

NGUYEN, QUANG

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 10/23/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/445,604

Applicant(s)

ABATANGELO ET AL.

Examiner

Quang Nguyen, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on July 31, 2002.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 122-161 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 122-161 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

The request filed on July 31, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/445604 is acceptable and a CPA has been established. An action on the CPA follows.

Applicants' amendment filed on June 03, 2002 in Paper No. 16 has been entered.

Claims 122-161 are pending in the present application, and they are examined on the merits herein.

Claim Objections

Claims 122 and 157 are objected to because of the following informalities: the term "autocrosslinked" is misspelled. Appropriate correction is required.

Claims 131 and 133 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because the process for preparing a biological material according to claim 123 is not necessarily limited to the use a hyaluronic acid derivative recited in claim 123, but to any hyaluronic acid derivative.

Claims 153 and 155 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s)

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in proper dependent form, or rewrite the claim(s) in independent form. This is because the process for preparing a biological material according to claim 144 or claim 145 is not necessarily limited to the use a hyaluronic acid derivative recited in claim 144, but to any hyaluronic acid derivative.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 122-130, 132, 134-152, 154, 156 and 159-160 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 122 and its dependent claims contain an improper Markush language by reciting "said matrix comprising a hyaluronic acid derivative selected from the group consisting of: an ester of hyaluronic acid....; an autocrosslinked ester of hyaluronic acid....; ahmiester of succinic acid or a heavy metal salt of the hemiester of succinic acid with hyaluronic acid....; An O- or N-sulphated hyaluronic acid...". It is unclear whether the hyaluronic acid derivative is selected from each of the recited hyaluronic acid derivatives or various combinations of the hyaluronic acid derivatives and which combinations? The metes and bounds of the claims are not clearly determined. A term - - and - - should be inserted prior to the phrase "An O- or N-sulphated hyaluronic acid..." to over this rejection. Similarly claims 144, 157, 159 and their dependent claims

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are rejected for the same reasons because they contain an improper Markush language.

Claims 129-130 recite the limitation "component (b)" in line 2 of the claims. There is insufficient antecedent basis for this limitation in the claim.

Claim 132 recites the limitation "step (i)" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claims 135-141 recite the limitation "component (a)" in line 2 of the claims. There is insufficient antecedent basis for this limitation in the claim.

Claims 142-143 recite the limitation "wherein (a)" in line 2 of the claims. There is insufficient antecedent basis for this limitation in the claim.

Claims 151-152 recite the limitation "component (b)" in line 2 of the claims. There is insufficient antecedent basis for this limitation in the claim.

Claims 154 recites the limitation "step (i)" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claims 122, 126, 128-129, 134, 138-141, 144, 148, 150-151 and 156-161 are rejected under 35 U.S.C. 102(b) as being anticipated by Bellini et al. (WO 96/37519 with a published date of 28 November 1996; IDS).

It is noted that for composition claims, the intended use is not given any patentable weight in view of the prior art.

Bellini et al. teach a polysaccharide hydrogel material consisting of a crosslinked product of a functionalized derivative of alginic acid or hyaluronic acid, whose carboxylic groups are partially esterified (preferably 75% of the carboxylic groups) with an unsaturated aliphatic or an araliphatic alcohol, and the remaining carboxylic groups are partially salified with a cation selected from the group consisting of alkaline, alkaline earth metal cation or with tetraalkylammonium (page 2, first paragraph and page 4, lines 21-26). Additionally Bellini et al. teach that the hydrogel material can be prepared in the form of fibers, films, membranes, threads, gauzes and sponges, which are three dimensional objects or matrix (page 2, lines 16 and page 6, lines 1-10). Moreover, Bellini et al. teach that the hydrogel material can be used as supports of human cells such as keratinocytes, fibroblasts, osteocytes, chondrocytes, urocytes, stem cells, endothelial cells, Kupfer's and Langerhan's cells (page 6, lines 11-14). It should be noted that the endothelial cells, Kupfer's and Langerhan's cells growing on the hydrogel material support of Bellini et al. are indistinguishable from autologous or homologous endothelial and glandular cell lines claimed by Applicants.

Accordingly, Bellini et al. teachings meet all limitations recited in the claims, and thus Bellini et al. anticipate the instantly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on June 03, 2002 in Paper No. 16 (pages 10-11) have been fully considered.

Applicants argue that "ester of hyaluronic acid wherein part or all of the carboxylic groups are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic or heterocyclic series" refers to a linear polysaccharide, in which some or all of the carboxy groups are esterified with the indicated alcohol, and therefore the compounds of the presently claimed invention do not encompass the cross-linked derivative of a hyaluronic acid ester product of Bellini et al. Applicants further argue that the esters of hyaluronic acid disclosed in U.S. 4,851,521 and 5,202,431 (class A compound in the claims) do not refer in any way to crosslinked derivatives of hyaluronic acid such as those of Bellini et al., and that Bellini et al. disclosed that the esters of hyaluronic acid in US 4,851,521 are the precursors of their product. With respect to the hyaluronic acid derivatives of class B, together with the submitted Declaration under 1.132, Applicants argue that the hyaluronic acid chains are cross-linked together directly without the presence of a "spacer" molecular bridge because part of the carboxy groups of the D-glucuronic residue react directly with the hydroxy functions belonging to the same chain or to the next HA chain, forming an ester-type bond. Therefore, the polysaccharides of class B of the presently claimed invention have completely different chemical structures and physical properties from the hydrogel material of Bellini et al. Applicants' arguments are respectfully found to be unpersuasive because the claims are

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not limited to a matrix comprising a hyaluronic acid derivative selected from class A compound without any crosslinking or from class B compound specifically without any "spacer" molecular bridge. With respect to compound A, the claims recite a matrix comprising a hyaluronic acid derivative which is an ester of hyaluronic acid wherein part or all of the carboxylic groups of said hyaluronic acid are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic series, the matrix of Bellini et al. also comprises an ester of hyaluronic acid wherein part or all of the carboxylic groups of said hyaluronic acid are esterified with alcohols of the aliphatic or araliphatic alcohol, and therefore the matrix of Bellini et al. meets the recited limitation of the claims. Thus, it is apparent that the polysaccharide hydrogel material of Bellini is a species encompassed within the broad scope of a biological material of the instantly claimed invention.

Accordingly, claims 122, 126, 128-129, 134, 138-141, 144, 148, 150-151 and 156-161 are rejected for the reasons set forth above.

Claims 122, 128-130, 134, 139-144, 150-152 and 156-161 are rejected under 35 U.S.C. 102(b) as being anticipated by Abatangelo et al. (WO97/18842) as evidenced by della Valle et al. (U.S. Patent No. 4,851,521; Cited previously) or Dorigatti et al. (U.S. Patent No. 5,520,916; Cited previously).

It is noted that for composition claims, the intended use is not given any patentable weight in view of the prior art.

Abatangelo et al. teach a biologic material comprising: a) an efficient culture of autologous or homologous bone marrow stem cells partially or completely differentiated

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into connective tissue specific cells such as endothelial cells, chondrocytes, osteoblasts, fibroblasts and others, and b) a three dimensional biocompatible and biodegradable matrix consisting of a hyaluronic acid derivative as those described by della Valle et al. and/or Dorigatti et al. (see abstract, line 20 on page 6 continues to line 17 of page 7). The hyaluronic acid derivatives of della Valle et al. and Dorigatti et al. are hyaluronic acid esters disclosed by the presently claimed invention (see the issued patents), and they can be in the form of non woven tissue, sponges, granules, microspheres, guide channels and gauzes (page 7, lines 2-4). Abatangelo et al. further teach that the biologic material is used for tissue grafts.

Accordingly, Abatangelo et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 122, 129-130, 144 and 151-152 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bellini et al. (WO 96/37519) in view of Cialdi et al. (U.S. Patent 6,027,741; Cited previously).

Bellini et al. teach a polysaccharide hydrogel material consisting of a crosslinked product of a functionalized derivative of alginic acid or hyaluronic acid, whose carboxylic groups are partially esterified (preferably 75% of the carboxylic groups) with an unsaturated aliphatic or an araliphatic alcohol, and the remaining carboxylic groups are partially salified with a cation selected from the group consisting of alkaline, alkaline earth metal cation or with tetraalkylammonium (page 2, first paragraph and page 4, lines 21-26). Additionally Bellini et al. teach that the hydrogel material can be prepared in the form of fibers, films, membranes, threads, gauzes and sponges, which are three dimensional objects or matrix (page 2, lines 16 and page 6, lines 1-10). Moreover, Bellini et al. teach that the hydrogel material can be used as supports of human cells such as keratinocytes, fibroblasts, osteocytes, chondrocytes, urocytes, stem cells, endothelial cells, Kupfer's and Langerhan's cells (page 6, lines 11-14). It is noted that the endothelial cells, Kupfer's and Langerhan's cells growing on the hydrogel material support of Bellini et al. are indistinguishable from autologous or homologous endothelial and glandular cell lines recited in the claims. Bellini et al. do not teach that the hydrogel material can be prepared in the form of a nonwoven fabric or the use of sulfated hyaluronic acid to support the aforementioned human cells.

Cialdi et al. disclose that sulfated hyaluronic acid, hyaluronate esters and salts thereof can be used to prepare biomaterials in various forms such as gauzes, threads, gels, hydrogels, sponges, membranes, non-woven tissues and microspheres, all of which are three dimensional objects or matrix (See abstract and column 14, lines 53-60). Furthermore, Cialdi et al. teach that human umbilical vein endothelial cells proliferate and exhibit better growth in culture medium containing sulfated hyaluronic acid than cells cultured in the medium containing hyaluronic acid or control medium (See example 16, columns 14 and 15).

Accordingly, at the time of the instant invention it would have been obvious to an ordinary skilled artisan to use hyaluronate esters, sulfated hyaluronic acid and salts thereof in any of the form of gauzes, threads, gels, hydrogels, sponges, non-woven tissues, microspheres as supports for endothelial cells, Kupfer's and Langerhan's cells because Bellini et al. already teach that polysaccharide hydrogel materials composing of crosslinked products of functionalized derivatives of hyaluronic acids can be used as supports for such cells. One of ordinary skilled in the art would have been motivated to use supports made up of sulfated hyaluronic acid disclosed by Cialdi et al., because Cialdi et al. already demonstrate in tissue culture that at least for endothelial cells, sulfated hyaluronic acid promotes the proliferation of endothelial cells. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on June 03, 2002 in Paper No. 16 (pages 11-13) have been fully considered.

With respect to the combined references of Bellini et al. (WO 96/37519) and Cialdi et al. (U.S. 6,027,741), Applicants argue that Bellini et al. do not teach that their described material is a better support for the growth and proliferation of fragile cells compared to other materials usually employed as substrates for anchorage dependent cells. The hyaluronic acid derivative of Bellini et al. also differs from that disclosed of the presently claimed invention. Applicants further argue that Bellini et al. do not disclose that the hydrogel material is able to promote proliferation of the cells. Therefore, Bellini's deficiencies can not be overcome by the combined teachings with Cialdi et al.

Applicants' arguments are found unpersuasive for the following reasons: Firstly, the hyaluronic acid derivative of the instant broadly claimed invention encompasses the hyaluronic acid derivative taught by Bellini et al. for the reasons already set forth in the Response to the rejection of claims 122, 125-126, 128-129, 134, 138-141, 144, 147-148, 150-151 and 156-161 above. Secondly, Bellini et al. clearly teach that their hydrogel material can be used as supports of human cells including endothelial cells, Kupfer's and Langerhan's cell. There is no recitation in the pending claims that require the cells to proliferate on the matrix. Moreover, there is no factual evidence that the cells would not grow on the hydrogel material taught by Bellini et al. Please note that an embodiment of the pending claims encompasses the same teachings of Bellini et al.,

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should Applicants doubt that the hydrogel material taught by Bellini et al. can support the proliferation of cells, then Applicants question the enablement of an embodiment of the present broadly claimed invention.

With respect to the reference of Cialdi et al., Cialdi et al. clearly teach that at the effective filing date of the present application sulfated hyaluronic acid, hyaluronate esters and salts thereof can be used to prepare biomaterials in various forms such as gauzes, threads, hydrogels, sponges, membranes, non-woven tissues and microspheres. Therefore, it would also have been obvious and within the scope of skilled for an ordinary artisan to modify the hydrogel material taught by Bellini et al. in the form of a non-woven fabric, since the hydrogel material of Bellini et al. can be prepared in the form of fibers, films, membranes, threads, guazes and sponges.

With respect to Applicants' arguments that Cialdi et al. do not disclose that O-sulfated hyaluronic acid derivatives of class E can be used as substrates for the growth of cells, and that example 14 of Cialdi et al. would not induce a person of skilled in the art to use such material for the growth of endothelial cells, Examiner would like to point out that Cialdi et al. specifically teach "The new biopolymers of the present invention can also be used to advantage in cell growth processes, in controlled drug release systems" (col. 3, lines 37-49). Moreover, Cialdi et al. teach that the disclosed biopolymers can be prepared in a three dimensional forms such as threads, sponges, gauzes, membranes, non-woven fabrics et al., therefore it would have been obvious that one of ordinary skilled artisan would have been motivated to use the disclosed biopolymers in three dimensional forms to support the growth of endothelial cells.

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Especially, Bellini et al. already taught that numerous cell types including endothelial cells can grow on supports comprised of crosslinked hyaluronic acid esters. It should be further noted that the teachings of Cialdi et al. are not limited by example 4.

Accordingly, claims 122, 129-130, 144 and 151-152 are rejected for the reasons set forth above.

Claims 122, 125, 131, 133, 144, 147, 153 and 155 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bellini et al. (WO 96/37519) in view of Williams et al. (U.S. Patent No. 5,131,907).

Bellini et al. teach a polysaccharide hydrogel material consisting of a crosslinked product of a functionalized derivative of alginic acid or hyaluronic acid, whose carboxylic groups are partially esterified (preferably 75% of the carboxylic groups) with an unsaturated aliphatic or an araliphatic alcohol, and the remaining carboxylic groups are partially salified with a cation selected from the group consisting of alkaline, alkaline earth metal cation or with tetraalkylammonium (page 2, first paragraph and page 4, lines 21-26). Additionally Bellini et al. teach that the hydrogel material can be prepared in the form of fibers, films, membranes, threads, gauzes and sponges, which are three dimensional objects or matrix (page 2, lines 16 and page 6, lines 1-10). Moreover, Bellini et al. also teach that the hydrogel material can be used as supports of human cells such as keratinocytes, fibroblasts, osteocytes, chondrocytes, urocytes, stem cells, endothelial cells, Kupfer's and Langerhan's cells (page 6, lines 11-14). It should be noted that the endothelial cells, Kupfer's and Langerhan's cells growing on the hydrogel

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material support of Bellini et al. are indistinguishable from autologous or homologous endothelial and glandular cell lines recited in the claims. Bellini et al. do not teach explicitly the process of making the hydrogel material supports containing the aforementioned cells, particularly the isolation of endothelial cells from human umbilical vein and amplifying the endothelial cells on collagen treated dishes prior to seeding the endothelial cells onto the hydrogel support. However, at the effective filing date of the present application, Williams et al. teach that endothelial cells isolated from various sources including human umbilical veins using a proteolytic enzyme such as collagenase, and that isolated endothelial cells cultured on interstitial collagens can undergo proliferation are known in the art (see background of the invention, particularly col. 4, lines 42-56; Fig. 1).

Accordingly, at the effective filing date of the present application, it would have been obvious and within the scope of skilled for an ordinary skilled artisan to isolate endothelial cells from a human umbilical vein through the use of collagenase digestion and expanding the isolated endothelial cells through culturing them on culture dishes coated with interstitial collagens known in the art as taught by Williams et al., prior to seeding the proliferated endothelial cells onto the hydrogel material for preparing the hydrogel support containing endothelial cells as taught by Bellini et al. One of ordinary skill artisan would have been motivated to carry out the above modification simply to obtain sufficient number of isolated endothelial cells for seeding on the hydrogel material of Bellini et al.

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Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Examiner would like to point out the article of Jaffe et al. (J. Clin. Invest. 52:2745-2756, 1973; IDS) who teach the isolation of human endothelial cells derived from umbilical veins by collagenase digestion, and the article of Madri et al. (J. Cell Biology 97:153-165, 1983; IDS) who teach that when capillary endothelial cells were grown on interstitial collagens, they underwent proliferation.

Conclusions

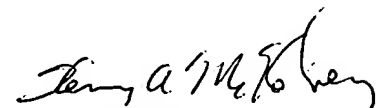
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

Quang Nguyen, Ph.D.


TERRY MCKELVEY
PRIMARY EXAMINER